

characteristics of an endogenous gene or a given cell
line

INVENTOR: **Scott C. Chappel**, Jamaica Plain, MA

ASSIGNEE: Applied Research Systems*Aris Holding N.V., Curaçao,
Netherlands Antilles (foreign corp.)

APPL-NO: 07/893,447

DATE FILED: May 28, 1992

ART-UNIT: 184

PRIM-EXMR: Robert A. Wax

ASST-EXMR: Miguel Escallon

LEGAL-REP: Browdy and Neimark

=> log y

U.S. Patent & Trademark Office LOGOFF AT 09:50:34 ON 07 NOV 94

+++

OK

ATZ

ATZ

OK

ATH

ATH

OK

BEST AVAILABLE COPY

102,390

5422 HOMOLOGOUS
8035 RECOMBINAT?

L1 260 HOMOLOGOUS(W)RECOMBINAT?
=> s 11 and regulatory(2w)element?

6302 REGULATORY
762645 ELEMENT?

220 REGULATORY(2W)ELEMENT?

L2 24 L1 AND REGULATORY(2W)ELEMENT?
=> s 12 and (exogenous or heterologous)

2667 EXOGENOUS
1676 HETEROLOGOUS

L3 19 L2 AND (EXOGENOUS OR HETEROLOGOUS)
=> s 13 and (exogenous or heterologous) (2w)regulatory(w)element?

2667 EXOGENOUS
1676 HETEROLOGOUS
6302 REGULATORY

762645 ELEMENT?

1 (EXOGENOUS OR HETEROLOGOUS) (2W)REGULATORY(W)ELEMENT?

L4 0 L3 AND (EXOGENOUS OR HETEROLOGOUS) (2W)REGULATORY(W)ELEMENT?
=> s (exogenous or heterologous) (2w)regulatory(w)element?

2667 EXOGENOUS
1676 HETEROLOGOUS
6302 REGULATORY

762645 ELEMENT?

L5 1 (EXOGENOUS OR HETEROLOGOUS) (2W)REGULATORY(W)ELEMENT?
=> d 15 cit,ab

1. 5,242,812, Sep. 7, 1993, Method for production and purification of hepatitis B vaccine; Zeev Even-Chen, 435/70.3; 424/88, 89; 435/69.3; 530/395, 412, 414, 415, 416, 417, 806; 935/65 [IMAGE AVAILABLE]

US PAT NO: 5,242,812 [IMAGE AVAILABLE]

L5: 1 of 1

ABSTRACT:

Processes are provided for producing purified, hepatitis B surface antigen particles in mammalian cells which comprise culturing mammalian cells which produce the particles in a culture medium supplemented with a serum free of high molecular weight contaminant proteins and recovering the purified, hepatitis B surface antigen particles.

Removal of molecules having a molecular weight greater than about 3.times.10.sup.5 daltons by prefractionation, for example, allows cells to be grown in culture media containing high levels of fetal calf serum, removes high molecular weight contaminant proteins which may be inhibitory to cell growth and simplifies purification of HBsAg since high molecular weight contaminant proteins are the major contaminants removed by purification processes.

=> +++

OK

ATZ

ATDT
OK
ATDT305-9488

ATDT305-9488
CONNECT 1200

Enter terminal type or "M" for menu - VT102

the expression of proteolytically sensitive recombinant products. The isolation and characterization of additional genes from species of the genus *Pichia* is also described, as well as uses therefore.
=> s 13 and amplifi?

188041 AMPLIFI?

L6 60 L3 AND AMPLIFI?

=> wild(w)type?

'WILD(W)TYPE?' IS NOT A RECOGNIZED COMMAND

=> s 16 and wild(w)type?

8105 WILD

1262404 TYPE?

1957 WILD(W)TYPE?

L7 41 L6 AND WILD(W)TYPE?

=> d 17 1-41 cit

1. 5,367,060, Nov. 22, 1994, Structure, production and use of heregulin; Richard L. Vandlen, et al., 530/399, 350 [IMAGE AVAILABLE]

2. 5,366,874, Nov. 22, 1994, Molecular cloning and expression of biologically-active diphtheria toxin receptor; Leon Eidels, et al., 435/69.1, 7.1, 7.2, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

3. 5,364,934, Nov. 15, 1994, Plasma carboxypeptidase; Dennis T. Drayna, et al., 536/23.2; 435/240.2, 252.3, 320.1 [IMAGE AVAILABLE]

4. 5,364,769, Nov. 15, 1994, Nucleic acid encoding neurotrophic factor four (NT-4), vectors, host cells and methods of production; Arnon Rosenthal, 435/69.1, 69.4, 240.1, 240.2, 320.1; 536/23.5, 23.51 [IMAGE AVAILABLE]

5. 5,350,671, Sep. 27, 1994, HCV immunoassays employing C domain antigens; Michael Houghton, et al., 435/5, 6, 975; 436/512, 518; 530/300, 326, 327, 328, 812, 826; 930/220, 223 [IMAGE AVAILABLE]

6. 5,348,886, Sep. 20, 1994, Method of producing recombinant eukaryotic viruses in bacteria; Stephen C. Lee, et al., 435/320.1, 69.1, 172.3, 252.3, 252.33; 536/23.1 [IMAGE AVAILABLE]

7. 5,346,991, Sep. 13, 1994, Tissue factor mutants useful for the treatment of myocardial infarction and coagulopathic disorders; Soumitra Roy, et al., 530/350; 435/172.3; 530/381, 829 [IMAGE AVAILABLE]

8. 5,338,665, Aug. 16, 1994, Peptide library and screening method; Peter J. Schatz, et al., 435/6, 7.32, 7.37, 172.3, 252.3, 252.33, 320.1; 935/73, 79, 80 [IMAGE AVAILABLE]

9. 5,324,663, Jun. 28, 1994, Methods and products for the synthesis of oligosaccharide structures on glycoproteins, glycolipids, or as free molecules, and for the isolation of cloned genetic sequences that determine these structures; John B. Lowe, 435/320.1, 69.1, 70.3, 172.3, 193, 240.2; 536/23.2; 935/14, 32, 70 [IMAGE AVAILABLE]

receptor; Gary L. Stiles, et al., 435/252.3, 69.1, 320.1; 536/23.5 [IMAGE AVAILABLE]

11. 5,316,931, May 31, 1994, Plant viral vectors having heterologous subgenomic **promoters** for systemic expression of foreign genes; Jon Donson, et al., 435/172.3, 69.1, 70.1, 320.1; 536/23.72, 24.1; 800/205; 935/25, 57, 64, 67 [IMAGE AVAILABLE]

12. 5,310,668, May 10, 1994, Varicella-zoster virus as a live recombinant vaccine; Ronald W. Ellis, et al., 424/199.1, 230.1; 435/172.3, 235.1, 320.1; 935/32, 57, 65 [IMAGE AVAILABLE]

13. 5,310,661, May 10, 1994, Nucleic acid encoding the .alpha. chain prodomains of inhibin and method for synthesizing polypeptides using such nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3, 320.1; 536/23.5, 23.51; 935/11 [IMAGE AVAILABLE]

14. 5,306,631, Apr. 26, 1994, Compositions and method for inhibition of HIV production; Gail Harrison, et al., 435/172.3, 240.2, 320.1; 935/56, 71 [IMAGE AVAILABLE]

15. 5,286,654, Feb. 15, 1994, Detection and purification of activin polypeptide; Edward T. Cox, et al., 436/501, 536; 530/388.22, 395, 413 [IMAGE AVAILABLE]

16. 5,262,177, Nov. 16, 1993, Recombinant viruses encoding the human melanoma-associated antigen; Joseph P. Brown, et al., 435/235.1; 424/185.1, 199.1, 232.1; 435/69.3, 172.3, 240.2, 252.3, 252.33, 320.1; 530/350; 536/23.5; 935/9, 32, 41, 57, 65, 70, 73 [IMAGE AVAILABLE]

17. 5,256,770, Oct. 26, 1993, Oxidation resistant thrombomodulin analogs; Charles B. Glaser, et al., 530/381; 435/69.6; 530/380 [IMAGE AVAILABLE]

18. 5,242,829, Sep. 7, 1993, Recombinant pseudorabies virus; Dennis L. Panicali, et al., 435/320.1; 424/199.1, 229.1, 232.1; 435/69.1, 69.3, 172.3 [IMAGE AVAILABLE]

19. 5,223,610, Jun. 29, 1993, Cholera toxin gene regulated by growth hormone **promoter**; Frank H. Burton, et al., 536/24.1; 435/69.2, 172.3, 320.1 [IMAGE AVAILABLE]

20. 5,223,408, Jun. 29, 1993, Method for making variant secreted proteins with altered properties; David V. Goeddel, et al., 435/69.3, 69.4, 69.52, 69.6, 69.7, 172.3, 189, 195, 215, 216, 226 [IMAGE AVAILABLE]

21. 5,216,126, Jun. 1, 1993, Receptor polypeptides and their production and uses; Edward T. Cox, et al., 530/350, 388.22, 389.1 [IMAGE AVAILABLE]

22. 5,215,893, Jun. 1, 1993, Nucleic acid encoding the ba chain prodomains of inhibin and method for synthesizing polypeptides using such nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3, 320.1; 536/23.5, 23.51; 935/11 [IMAGE AVAILABLE]

23. 5,206,161, Apr. 27, 1993, Human plasma carboxypeptidase B; Dennis T. ... [IMAGE AVAILABLE]

24. 5,202,238, Apr. 13, 1993, Production of chimeric antibodies by
homologous **recombination**;
H. Perry Fell, Jr., et al., 435/69.6,
69.7, 70.1, 70.21, 172.3, 320.1; 530/387.3, 388.8; 536/23.53; 935/15, 111
[IMAGE AVAILABLE]

25. 5,198,346, Mar. 30, 1993, Generation and selection of novel
DNA-binding proteins and polypeptides; Robert C. Ladner, et al.,
435/69.1, 172.3, 252.3, 320.1 [IMAGE AVAILABLE]

26. 5,194,376, Mar. 16, 1993, Baculovirus expression system capable of
producing foreign gene proteins at high levels; C. Yong Kang, 435/69.1;
204/180.1, 182.8, 299R; 435/172.3, 320.1 [IMAGE AVAILABLE]

27. 5,186,933, Feb. 16, 1993, Synthesis and immunogenicity of rotavirus
genes using a baculovirus expression system; Mary K. Estes, 424/215.1;

435/172.1, 172.3, 235.1, 320.1; 530/826; 935/24, 32, 57, 65 [IMAGE
AVAILABLE]

28. 5,180,675, Jan. 19, 1993, Recombinant fowlpox virus; Robert
Drillien, et al., 435/235.1; 424/199.1, 232.1; 435/236, 320.1; 935/32
[IMAGE AVAILABLE]

29. 5,174,993, Dec. 29, 1992, Recombinant avipox virus and immunological
use thereof; Enzo Paoletti, 424/199.1, 207.1, 210.1, 214.1, 222.1, 224.1,
231.1, 232.1; 435/235.1, 320.1; 935/32, 57, 65 [IMAGE AVAILABLE]

30. 5,141,742, Aug. 25, 1992, Vaccines against melanoma; Joseph P.
Brown, et al., 424/186.1, 277.1; 435/69.3, 70.1, 71.1, 71.2; 530/350,
395; 536/23.5 [IMAGE AVAILABLE]

31. 5,098,837, Mar. 24, 1992, Macrolide biosynthetic genes for use in
streptomyces and other organisms; Robert J. Beckmann, et al., 435/172.3,
71.2, 76, 91.41, 91.5, 169, 172.1, 252.35, 320.1, 886; 536/23.2, 23.7;
935/6, 9, 22, 29, 59, 60, 61, 66, 72, 75 [IMAGE AVAILABLE]

32. 5,093,258, Mar. 3, 1992, Recombinant fowlpox virus and recombination
vector; Lawrence K. Cohen, et al., 435/235.1; 424/199.1, 232.1;
435/172.3, 320.1; 935/6, 32, 65 [IMAGE AVAILABLE]

33. 5,089,396, Feb. 18, 1992, Nucleic acid encoding .beta. chain
prodomains of inhibin and method for synthesizing polypeptides using such
nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3,
320.1; 536/23.51; 935/11 [IMAGE AVAILABLE]

34. 5,049,488, Sep. 17, 1991, Method and nucleic acid for the
preparation of lecithin:cholesterol acyltransferase; Bradford W. Baer, et
al., 435/6, 172.3, 803; 436/501; 530/397; 536/24.31; 935/78 [IMAGE
AVAILABLE]

35. 5,041,379, Aug. 20, 1991, Heliothis expression systems; Malcolm J.
Fraser, et al., 435/235.1, 69.1, 70.1, 172.3, 240.2, 320.1; 536/23.2,
23.6, 23.72; 935/3, 6, 9, 22, 33, 34, 47, 48, 59, 60, 61, 66, 70 [IMAGE
AVAILABLE]

36. 5,030,576, Jul. 9, 1991, Receptors for efficient determination of

ligands and their antagonists or agonists; Thomas J. Dull, et al.,
435/69.7; 69.1; 530/350, 388.22; 536/23.1, 24.1 [IMAGE AVAILABLE]

37. 5,017,487, May 21, 1991, Vaccinia DNA; Hendrik G. Stunnenberg, et
al., 435/172.3, 235.1, 320.1, 948; 536/24.1; 935/6, 32, 34, 57 [IMAGE
AVAILABLE]

38. 4,920,209, Apr. 24, 1990, Oral vaccines; Alan R. Davis, et al.,
435/235.1; 424/199.1, 227.1, 233.1; 435/69.3, 172.3 [IMAGE AVAILABLE]

39. 4,885,251, Dec. 5, 1989, Recombinant DNA expression vectors and DNA
compounds which encode isopenicillin N synthetase; Thomas D. Ingolia, et
al., 435/183, 172.3, 252.2, 252.3, 252.33, 252.35, 254.11, 254.5, 320.1;
536/23.2, 23.7; 935/14, 27, 34, 60, 68, 72 [IMAGE AVAILABLE]

40. 4,859,609, Aug. 22, 1989, Novel receptors for efficient

determination of ligands and their antagonists or agonists; Thomas J.
Dull, et al., 436/501; 435/7.22, 7.31, 7.9, 968; 436/63, 503, 537;
530/402, 806, 808; 935/81, 109 [IMAGE AVAILABLE]

41. 4,798,885, Jan. 17, 1989, Compositions of hormonally active human
and porcine inhibin containing an .alpha. chain and 62 chain; Anthony J.
Mason, et al., 530/350; 930/10, 260, DIG.530, DIG.821 [IMAGE AVAILABLE]
=> log y

U.S. Patent & Trademark Office LOGOFF AT 09:46:14 ON 27 FEB 95

+++

OK

ATZ

ATZ

OK

ATH

ATH

OK

```

L1          0 CHAPPEL, SCOTT/IN
=> e chapel, scott/in
E1          1      CHAPPEL, LARRY R/IN
E2          5      CHAPPEL, RAYMOND M/IN
E3          0 --> CHAPPEL, SCOTT/IN
E4          6      CHAPPEL, SCOTT C/IN
E5          1      CHAPPEL, TIMOTHY M/IN
E6          3      CHAPPELEAR, ROBERT N/IN
E7          1      CHAPPELIE, NORMAN A/IN
E8          1      CHAPPELIE, NORMAN ANDREW/IN
E9          4      CHAPPELL, ALBERT R/IN
E10         1      CHAPPELL, ALICE M/IN
E11         3      CHAPPELL, ANTHONY G/IN
E12         2      CHAPPELL, AUSTIN/IN
=> s e4
L2          6 "CHAPPEL, SCOTT C"/IN
=> d 12 1-6 cit

```

1. 5,352,779, Oct. 4, 1994, Site-directed mutagenesisTM modified DNA encoding glycoprotein hormones and methods of use; ****Scott C. Chappel**, et al.**, 536/23.51; 435/69.1, 69.4, 252.3, 320.1; 530/399; 536/23.5 [IMAGE AVAILABLE]

2. 5,272,071, Dec. 21, 1993, Method for the modification of the expression characteristics of an endogenous gene of a given cell line; ****Scott C. Chappel**, 435/172.3, 69.1, 172.1, 252.3, 320.1; 536/23.1, 24.3; 935/6, 23, 34, 42 [IMAGE AVAILABLE]**

3. 5,262,518, Nov. 16, 1993, Ovulation kit comprising FSH isoforms with varying half-lives; ****Scott C. Chappel**, 530/313; 435/975 [IMAGE AVAILABLE]**

4. 5,260,421, Nov. 9, 1993, Site-directed mutagenesis modified glycoprotein hormones; ****Scott C. Chappel**, et al.**, 530/397, 398, 399 [IMAGE AVAILABLE]

5. 5,240,832, Aug. 31, 1993, Heteropolymeric protein production methods; Christie A. Kelton, et al., 435/69.4, 69.1, 172.3, 240.2, 320.1; 536/23.1, 23.5, 23.51; 930/110; 935/6, 13, 34, 60, 61, 66, 70 [IMAGE AVAILABLE]

6. 5,087,615, Feb. 11, 1992, Novel method of ovulation induction in humans; ****Scott C. Chappel**, 514/21; 435/69.4; 514/12; 530/313, 324 [IMAGE AVAILABLE]**

=> d 11 2 leg

'L1' HAS NO ANSWERS

L1 0 SEA FILE=USPAT CHAPPEL, SCOTT/IN

=> d 12 2 leg

US PAT NO: 5,272,071 [IMAGE AVAILABLE]

L2: 2 of 6

DATE ISSUED: Dec. 21, 1993

TITLE: Method for the modification of the expression

Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing

29185 SILENT

5616614 GENE?

S1 1544 SILENT (3W) GENE?

?s s1 and homologous(w) recombination

1544 S1

194232 HOMOLOGOUS

161210 RECOMBINATION

14283 HOMOLOGOUS (W) RECOMBINATION

S2 13 S1 AND HOMOLOGOUS (W) RECOMBINATION

?nd s2

...completed examining records

S3 10 RD S2 (unique items)

?t s3/6/1-10\

>>>'10\' not recognized as item list

?t s3/6/1-10

3/6/1 (Item 1 from file: 5)

10486906 BIOSIS Number: 96086906

REARRANGEMENT OF SAPA HOMOLOGS WITH CONSERVED AND VARIABLE REGIONS IN
CAMPYLOBACTER-FETUS

3/6/2 (Item 1 from file: 76)

1926733 82003576171

Method for the modification of the expression characteristics of an
endogenous gene of a given cell line

3/6/3 (Item 1 from file: 434)

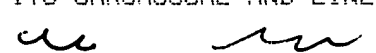
12503993 Genuine Article#: LR651 Number of References: 34

Title: USING SIMULTANEOUS, TANDEM GENE REPLACEMENTS TO STUDY EXPRESSION OF
THE MULTICOPY UBIQUITIN-FUSION (FUS) GENE FAMILY OF TRYPANOSOMA-CRUZI
(Abstract Available)

3/6/4 (Item 2 from file: 434)

11836719 Genuine Article#: JQ146 Number of References: 65

Title: THE RELAPSING FEVER AGENT BORRELIA-HERMSII HAS MULTIPLE COPIES OF
ITS CHROMOSOME AND LINEAR PLASMIDS (Abstract Available)



3/6/5 (Item 3 from file: 434)
11518152 Genuine Article#: HN934 Number of References: 23

Title: TRANS-ACTING FACTORS AND PROPERLY POSITIONED DNA ELEMENTS REPRESS
MATING-TYPE GENES IN FISSION YEAST (Abstract Available)

3/6/6 (Item 4 from file: 434)
11275465 Genuine Article#: GW053 Number of References: 58
Title: ONCOGENES RESULT IN GENOMIC ALTERATIONS THAT ACTIVATE A
TRANSCRIPTIONALLY SILENT, DOMINANTLY SELECTABLE REPORTER GENE (NEO) (
Abstract Available)

3/6/7 (Item 5 from file: 434)
10893241 Genuine Article#: FP319 Number of References: 48
Title: MODULATION OF GENE ACTIVITY BY CONSECUTIVE GENE TARGETING OF ONE
CREATINE-KINASE M-ALLELE IN MOUSE EMBRYONIC STEM-CELLS (Abstract
Available)

3/6/8 (Item 6 from file: 434)
10707719 Genuine Article#: FB733 Number of References: 25
Title: RECOMBINASE-MEDIATED GENE ACTIVATION AND SITE-SPECIFIC INTEGRATION
IN MAMMALIAN-CELLS (Abstract Available)

3/6/9 (Item 7 from file: 434)
09450572 Genuine Article#: U3655 Number of References: 32
Title: THE NATURALLY-OCCURRING SILENT INVERTASE STRUCTURAL GENE
SUC2-DEGREES CONTAINS AN AMBER STOP CODON THAT IS OCCASIONALLY READ
THROUGH

3/6/10 (Item 8 from file: 434)
08452243 Genuine Article#: K9586 Number of References: 64
Title: REPLICATION AND SEGREGATION OF PLASMIDS CONTAINING CIS-ACTING
REGULATORY SITES OF SILENT MATING-TYPE GENES IN
SACCHAROMYCES-CEREVISIAE ARE CONTROLLED BY THE SIR GENES

?t s3/7/2,3,6,7,8

3/7/2 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
(c) 1995 Cambridge Sci Abs. All rts. reserv.

1926733 82003576171

Method for the modification of the expression characteristics of an
endogenous gene of a given cell line

Chappel, S.C.

Applied Res. Syst. Ars Holding N.V., Curacao (Netherlands Antilles)

Publ: 21 Dec 1993 1993

Patent No.: US Patent 5,272,071

Language: English

Document Type: Patent

Subfile: 33 Medical and Pharmaceutical Biotechnology Abstracts

A method of activating a predetermined normally transcriptionally silent gene within the genome of a cell line so as to enable said cell line to express the gene product of said gene, comprising inserting a DNA construct

into said genome by homologous recombination, said DNA construct comprising a DNA regulatory segment capable of stimulating expression of said gene when operatively linked thereto and a DNA targeting segment homologous to a region of said genome within or proximal to said gene, wherein said construct is inserted such that said regulatory segment is operatively linked to said gene of interest.

3/7/3 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R)
(c) 1995 Inst for Sci Info. All rts. reserv.

12505993 Genuine Article#: LR651 Number of References: 34
Title: USING SIMULTANEOUS, TANDEM GENE REPLACEMENTS TO STUDY EXPRESSION OF
THE MULTICOPY UBIQUITIN-FUSION (FUS) GENE FAMILY OF TRYPANOSOMA-CRUZI
Author(s): GILLESPIE RD; AJIOKA J; SWINDLE J
Corporate Source: UNIV TENNESSEE CTR HLTH SCI,DEPT MICROBIOL & IMMUNOL,858
MADISON AVE/MEMPHIS//TN/38163; UNIV TENNESSEE CTR HLTH SCI,DEPT
MICROBIOL & IMMUNOL,858-MADISON AVE/MEMPHIS//TN/38163
Journal: MOLECULAR AND BIOCHEMICAL PARASITOLOGY, 1993, V60, N2 (AUG), P
281-292
ISSN: 0166-6851
Language: ENGLISH Document Type: ARTICLE

Abstract: Many genes in trypanosomes exist as members of multicopy gene families. Due to this fact it is frequently difficult to determine if specific members of a gene family are expressed. We describe here a strategy for simultaneous tandem gene replacement in T cruzi which leads to the replacement of the gene of interest by a silent reporter gene, the expression of which can be assayed in stable transformants. To determine if the FUS1 gene (one of 5 copies of the ubiquitin-fusion, FUS, gene family) was expressed, stable G418-resistant transformants were isolated in which the tandemly arrayed CUB2.65 and FUS1 genes were precisely replaced by the neomycin phosphotransferase (neo(r)) and chloramphenicol acetyltransferase (CAT) genes, respectively. All stable clones carrying the tandem gene replacements were shown to express the CAT activity indicating that FUS1 is expressed in mid-log epimastigotes. Northern blot analysis of parasites carrying the tandem gene replacements indicated that at least one other member of the FUS gene family is expressed and that there were no apparent polar effects on the expression of genes downstream of the replacement events. These experiments have demonstrated the utility of tandem gene replacements as a means of inserting a nonselected reporter gene into the chromosome, facilitating the molecular genetic analysis of the expression of multicopy gene families.

3/7/6 (Item 4 from file: 434)
DIALOG(R)File 434:SciSearch(R)
(c) 1995 Inst for Sci Info. All rts. reserv.

11275465 Genuine Article#: GW053 Number of References: 58
Title: ONCOGENES RESULT IN GENOMIC ALTERATIONS THAT ACTIVATE A
TRANSCRIPTIONALLY SILENT, DOMINANTLY SELECTABLE REPORTER GENE (NEO)

102390

6175 HOMOLOGOUS

8576 RECOMBINATION

L1 366 HOMOLOGOUS (3W) RECOMBINATION

=> s 11 and promoter?

20762 PROMOTER?

L2 325 L1 AND PROMOTER?

=> s 12 and eukaryotic (3w) cell?

2088 EUKARYOTIC

286683 CELL?

1263 EUKARYOTIC (3W) CELL?

L3 88 L2 AND EUKARYOTIC (3W) CELL?

=> s 13 and endogenous (w) target (w) gene?

5224 ENDOGENOUS

67961 TARGET

1052864 GENE?

1 ENDOGENOUS (W) TARGET (W) GENE?

L4 0 L3 AND ENDOGENOUS (W) TARGET (W) GENE?

=> s endogenous (w) target (w) gene?

5224 ENDOGENOUS

67961 TARGET

1052864 GENE?

L5 1 ENDOGENOUS (W) TARGET (W) GENE?

=> d 15 cit, ab

1. 5,324,660, Jun. 28, 1994, Genes which influence Pichia proteolytic activity, and uses therefor; Martin A. Gleeson, et al., 435/254.23, 69.1, 938 [IMAGE AVAILABLE]

US PAT NO: 5,324,660 [IMAGE AVAILABLE]

L5: 1 of 1

ABSTRACT:

The isolation and characterization of genes involved in proteolytic processing in species of the genus Pichia is described. The availability of such genes has enabled the generation of strains of Pichia which are deficient in proteolytic activity, which strains are useful as hosts for.

AUTHOR(S): DREWS RC; CHAN VW; SCHNIFFER LE
Corporate Source: HARVARD UNIV,BETH ISRAEL HOSP,CHARLES A DANA RES
INST/BOSTON//MA/02215; HARVARD UNIV,BETH ISRAEL HOSP,THORNDIKE

LAB/BOSTON//MA/02215; BETH ISRAEL HOSP,DEPT MED/BOSTON//MA/02215;
HARVARD UNIV,SCH MED/BOSTON//MA/02115

Journal: MOLECULAR AND CELLULAR BIOLOGY, 1992, V12, N1 (JAN), P198-206

Language: ENGLISH Document Type: ARTICLE

Abstract: Although oncogenes and tumor suppressor genes have been implicated in carcinogenesis and tumor progression, their relationship to the development of genomic instability has not been elucidated. To examine this role, we transfected oncogenes (polyomavirus middle [Py] and large T [MT and LT]) and adenovirus serotype 5 E1A) into two NIH 3T3-derived cell lines, EN/NIH 2-4 and EN/NIH 2-20. Both cell lines contain two stable integrants of a variant of the retrovirus vector pZipNeoSV (x)1 that has been modified by deletion of the enhancer elements from the long terminal repeats. DNA rearrangements activating the silent neomycin phosphotransferase gene (neo) present in these integrants were identified by selection of cells in the antibiotic G418. Whereas control-transfected EN/NIH cell lines do not yield G418-resistant subclones (GRSs), a fraction of oncogene-transfected EN/NIH 2-4 (8 of 19 Py MT, 5 of 17 Py LT, and 11 of 19 E1A) and 2-20 (7 of 15 Py MT) cell lines gave rise to GRSs at differing frequencies (0.33×10^{-6} to 46×10^{-6} for line 2-4 versus 0.11×10^{-6} to 1.3×10^{-6} for line 2-20) independent of cell generation time. In contrast, a distinctly smaller fraction of mutant Py MT-transfected EN/NIH cell lines (1 of 10 MT23, 1 of 10 MT1015, and 0 of 10 MT59b) resulted in GRSs. Southern analysis of DNA from selected oncogene-transfected GRSs demonstrated genomic rearrangements of neo-containing cellular DNA that varied in type (amplification and/or novel fragments) and frequency depending on the specific oncogene and EN/NIH cell line used in transfection. Furthermore, only one of the two neo-containing genomic loci present in both EN/NIH cell lines appeared to be involved in these genomic events. In addition to effects related to the genomic locus, these observations support a role for oncogenes in the development of genetic changes associated with tumor progression.

3/7/7 (Item 5 from file: 434)
DIALOG(R)File 434:SciSearch(R)
(c) 1995 Inst for Sci Info. All rts. reserv.

10857241 Genuine Article#: FP319 Number of References: 48
Title: MODULATION OF GENE ACTIVITY BY CONSECUTIVE GENE TARGETING OF ONE
CREATINE-KINASE M-ALLELE IN MOUSE EMBRYONIC STEM-CELLS
Author(s): VANDEURSEN J; LOVELLBADGE R; DERLEMANS F; SCHEPENS J; WIERINGA B
Corporate Source: CATHOLIC UNIV NIJMEGEN,DEPT CELL BIOL & HISTOL,POB
9101/6500 HB NIJMEGEN//NETHERLANDS/; CATHOLIC UNIV NIJMEGEN,DEPT CELL
BIOL & HISTOL,POB 9101/6500 HB NIJMEGEN//NETHERLANDS/; NATL INST MED
RES,EUKARYOT MOLEC GENET LAB/LONDON NW7 1AA//ENGLAND/
Journal: NUCLEIC ACIDS RESEARCH, 1991, V19, N10, P2637-2643
Language: ENGLISH Document Type: ARTICLE
Abstract: The cytosolic creatine kinases (CK's; EC 2.7.3.2) BB, BM and MM are dimeric isoenzymes which have an important role in energy metabolism and display characteristic tissue- and stage-specific patterns of expression in mammals. To study the functional role of the

distribution of the CK isoenzymes we have focussed on the modulation of expression of the genes encoding the individual B and M subunits, starting at the muscle creatine kinase (CKM) gene which is

transcriptionally inactive during early embryogenesis. Using repeated rounds of gene targeting in mouse embryonic stem (ES) cells, two types of mutant cell lines were obtained. First, we generated a cell line in which insertion of a neomycin resistance (neo(r)) gene had disrupted one of the CKM alleles. Subsequently, from this cell line, following introduction of an insertion type vector designed for replacement of the muscle specific CKM-enhancer by the constitutively acting polyoma virus enhancer PyF441, several independent doubly targeted clones were isolated which all had insertions in the previously neo-disrupted CKM allele. In some of these ES clones, the targeted enhancer replacement resulted in gene correction and functional activation of the silent CKM gene. Dimerisation between the ectopically expressed CKM subunits and CKB subunits which are normally present at high levels in ES cells, led to the formation of the BM isoform of CK in these clones.

3/7/8 (Item 6 from file: 434)
DIALOG(R)File 434:SciSearch(R)
(c) 1995 Inst for Sci Info. All rts. reserv.

10707719 Genuine Article#: FB733 Number of References: 25
Title: RECOMBINASE-MEDIATED GENE ACTIVATION AND SITE-SPECIFIC INTEGRATION
IN MAMMALIAN-CELLS
Author(s): OGORMAN S; FOX DT; WAHL GM
Corporate Source: SALK INST BIOL STUDIES,GENE EXPRESS LAB/LA
JOLLA//CA/92037
Journal: SCIENCE, 1991, V251, N4999, P1351-1355
Language: ENGLISH Document Type: ARTICLE
Abstract: A binary system for gene activation and site-specific integration, based on the conditional recombination of transfected sequences mediated by the FLP recombinase from yeast, was implemented in mammalian cells. In several cell lines, FLP rapidly and precisely recombined copies of its specific target sequence to activate an otherwise silent beta-galactosidase reporter gene. Clones of marked cells were generated by excisional recombination within a chromosomally integrated copy of the silent reporter. By the reverse reaction, integration of transfected DNA was targeted to a specific chromosomal site. The results suggest that FLP could be used to mosaically activate or inactivate transgenes for analysis of vertebrate development, and to efficiently integrate transfected DNA at predetermined chromosomal locations.

?logoff

06apr95 13:39:38 User214264 Session D64.2
\$0.60 0.020 Hrs File5
\$0.00 1 Type(s) in Format 6
\$0.00 1 Types
\$0.21 View Fee
\$0.81 Estimated cost File5
\$0.
30 0.010 Hrs File50
\$0.10 View Fee
\$0.40 Estimated cost AFile50
\$0.75 0.010 Hrs File76

File 1
\$0.00 1 Type(s) in Format 6
\$0.95 1 Type(s) in Format 7

\$0.95 2 Types

\$0.13 View FTZee

\$1.86 Estimated cost File76

\$2.28 0.038 Hrs File144

\$0.38 View Fee

\$2.66 Estimate

d cost File144

\$0.53 0.035 Hrs File155

\$0.36 View Fee

\$0.89 Estimated cost File155

\$0.24 0.004 Hrs File185

\$0.04 View Fee

\$0.28 Estimated cost File185

\$0.00 0.000 Hrs File295

\$0.01 View Fee

\$0.01 Estimated cost File295

\$3.51 0.039 Hrs File399

\$0.39 View Fee

\$3.90 Estimated cost File399

\$4.44 0

OK

L1 1060763 GENE?
s l1 and (silent or transcription?(2w)inactiv

MISSING OPERATOR 'L1 AN.'

=> s l1 and (silent or transcription?(2w)inactiv?)
6021 SILENT
4170 TRANSCRIPTION?
62500 INACTIV?
16 TRANSCRIPTION?(2W)INACTIV?

L2 4610 L1 AND (SILENT OR TRANSCRIPTION?(2W)INACTIV?)

=> s l2 and homologous(2w)recombin?tion
6257 HOMOLOGOUS
21705 RECOMBIN?

388 HOMOLOGOUS(2W)RECOMBIN?

L3 49 L2 AND HOMOLOGOUS(2W)RECOMBIN?

=> s l3 and regulatory(w)sequence?

7294 REGULATORY
256755 SEQUENCE?
579 REGULATORY(W)SEQUENCE?

L4 11 L3 AND REGULATORY(W)SEQUENCE?

=> d l4 1-11 cit,ab

1. 5,350,671, Sep. 27, 1994, HCV immunoassays employing C domain antigens; Michael Houghton, et al., 435/5, 6, 975; 436/512, 518; 530/300, 326, 327, 328, 812, 826; 930/220, 223 [IMAGE AVAILABLE]

US PAT NO: 5,350,671 [IMAGE AVAILABLE] L4: 1 of 11

ABSTRACT:

Immunoassays for the detection of antibodies to HCV are provided which employ "C" domain antigens. Immunoassay kits comprising such antigens are also provided.

2. 5,272,071, Dec. 21, 1993, Method for the modification of the expression characteristics of an endogenous **gene** of a given cell line; Scott C. Chappel, 435/172.3, 69.1, 172.1, 252.3, 320.1; 536/23.1, 24.3; 935/6, 23, 34, 42 [IMAGE AVAILABLE]

US PAT NO: 5,272,071 [IMAGE AVAILABLE] L4: 2 of 11

ABSTRACT:

Normally transcriptionally **silent** **genes** in a cell line or microorganism may be activated for expression by inserting a DNA regulatory element which is capable of promoting the expression of a normally expressed **gene** product in that cell or which is promiscuous, the regulatory element being inserted so as to be operatively linked with the normally **silent** **gene** in question. The insertion is accomplished by means of **homologous** **recombination** by creating a DNA construct including a segment having a DNA segment of the normally

****silent** **gene**** (targeting DNA) and the DNA regulatory element to induce ****gene**** transcription. The technique is also used to modify the expression characteristics of any endogenous ****gene**** of a given cell

line or microorganism.

3. 5,262,177, Nov. 16, 1993, Recombinant viruses encoding the human melanoma-associated antigen; Joseph P. Brown, et al., 435/235.1; 424/185.1, 199.1, 232.1; 435/69.3, 172.3, 240.2, 252.3, 252.33, 320.1; 530/350; 536/23.5; 935/9, 32, 41, 57, 65, 70, 73 [IMAGE AVAILABLE]

US PAT NO: 5,262,177 [IMAGE AVAILABLE] L4: 3 of 11

ABSTRACT:

Peptides or proteins related to a melanoma associated antigen are described. These are produced in large quantities via recombinant DNA techniques and/or by chemical synthetic methods. The peptides or proteins can be used as immunogens in vaccine formulations which can induce an immune response that selectively destroys melanoma cells in a vaccinated individual. Where the peptides or proteins are expressed by a recombinant virus, inactivated or live virus vaccine formulations may be prepared.

4. 5,223,254, Jun. 29, 1993, Respiratory syncytial virus: vaccines; Peter R. Paradiso, et al., 424/186.1, 211.1; 514/2, 8, 12 [IMAGE AVAILABLE]

US PAT NO: 5,223,254 [IMAGE AVAILABLE] L4: 4 of 11

ABSTRACT:

Polypeptides, nucleotides, and compositions useful for preparing diagnostic reagents for and vaccines against human Respiratory Syncytial Virus are disclosed. The polypeptides include short polypeptides which are related to a neutralizing and fusion epitope of the Respiratory Syncytial Virus fusion protein or a neutralizing epitope of the G protein.

5. 5,198,346, Mar. 30, 1993, ****Generation**** and selection of novel DNA-binding proteins and polypeptides; Robert C. Ladner, et al., 435/69.1, 172.3, 252.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,198,346 [IMAGE AVAILABLE] L4: 5 of 11

ABSTRACT:

Novel DNA-binding proteins, especially repressors of ****gene**** expression, are obtained by variegation of ****genes**** encoding known binding proteins and selection for proteins binding the desired target DNA sequence. A novel selection vector may be used to reduce artifacts. Heterooligomeric proteins which bind to a target DNA sequence which need not be palindromic are obtained by a variety of methods, e.g., variegation to obtain proteins binding symmetrized forms of the half-targets and heterodimerization to obtain a protein binding the entire asymmetric target.

6. 5,196,338, Mar. 23, 1993, Recombinant vectors for Haemophilus influenzae peptides and proteins; Algis Anilionis, et al., 435/252.3, 69.1, 69.7, 320.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,196,338 [IMAGE AVAILABLE] L4: 6 of 11

ABSTRACT:

Peptides and proteins related to an epitope comprising an outer membrane protein of Haemophilus influenzae are described. The peptides and proteins can be prepared by methods including novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides, proteins and fusion proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides, proteins, and fusion proteins in appropriate host cells. The peptides, proteins, fusion proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides, proteins and fusion proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides, proteins and fusion proteins in hybridization assays is also described.

7. 5,196,316, Mar. 23, 1993, Enzyme and DNA coding therefor; Yasuno Iwasaki, et al., 435/69.1, 68.1, 219, 232, 320.1; 530/350, 855; 536/23.2 [IMAGE AVAILABLE]

US PAT NO: 5,196,316 [IMAGE AVAILABLE] L4: 7 of 11

ABSTRACT:

The invention concerns a peptidylhydroxyglycine N-C lyase (PHL) catalyzing the reaction

$R-GlyOH.fwdarw.R-NH.sub.2$
wherein R represents a peptide residue, and GlyOH represents an .alpha.-hydroxyglycine residue linked to the C-terminus of said peptide R by an amide bond, a recombinant DNA molecule coding for a PHL, a method for the preparation of such a recombinant DNA molecule, processes for the preparation of PHL from a natural source or by means of the said recombinant DNA molecule, and the use of PHL for the preparation of an amidated peptide R-NH.sub.2.

8. 5,141,742, Aug. 25, 1992, Vaccines against melanoma; Joseph P. Brown, et al., 424/186.1, 277.1; 435/69.3, 70.1, 71.1, 71.2; 530/350, 395; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,141,742 [IMAGE AVAILABLE] L4: 8 of 11

ABSTRACT:

Peptides or proteins related to a melanoma associated antigen are described. These are produced in large quantities via recombinant DNA techniques and/or by chemical synthetic methods. The peptides or proteins can be used as immunogens in vaccine formulations which can induce an immune response that selectively destroys melanoma cells in a vaccinated individual. Where the peptides or proteins are expressed by a recombinant virus, inactivated or live virus vaccine formulations may be prepared.

9. 5,110,908, May 5, 1992, Haemophilus influenzae peptides and proteins;

Robert A. Deich, et al., 530/403, 435/71.1, 71.2, 187, 170, 171, 172.1, 820, 851; 530/333, 345, 350, 806, 808, 825 [IMAGE AVAILABLE]

US PAT NO: 5,110,908 [IMAGE AVAILABLE]

L4: 9 of 11

ABSTRACT:

Peptides and proteins related to an epitope comprising an outer membrane protein of *Haemophilus influenzae* are described. The peptides and proteins can be prepared by methods including novel and improved methods of purification from *H. influenzae* cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides and proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides and proteins in appropriate host cells. The peptides, proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against *H. influenzae* infections. The peptides and proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides and proteins in hybridization assays is also described.

10. 5,108,744, Apr. 28, 1992, Vaccines for *Haemophilus influenzae*; Robert A. Deich, et al., 424/190.1, 256.1; 514/2; 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,108,744 [IMAGE AVAILABLE]

L4: 10 of 11

ABSTRACT:

Peptides and proteins related to an epitope comprising an outer membrane protein of *Haemophilus influenzae* are described. The peptides and proteins can be prepared by methods including novel and improved methods of purification from *H. influenzae* cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequence encoding PBOMP-1 and PBOMP-2 related peptides and proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides and proteins in appropriate host cells. The peptides, proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against *H. influenzae* infections. The peptides and proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides and proteins in hybridization assays is also described.

11. 5,098,997, Mar. 24, 1992, Vaccines for *Haemophilus influenzae*; Algis Anilionis, et al., 530/350; 435/69.3, 69.7, 851; 530/405, 806, 825 [IMAGE AVAILABLE]

US PAT NO: 5,098,997 [IMAGE AVAILABLE]

L4: 11 of 11

ABSTRACT:

Peptides and proteins related to an epitope comprising an outer membrane protein of *Haemophilus influenzae* are described. The peptides and

proteins can be prepared by methods including novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors

containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides, proteins and fusion proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides, proteins, and fusion proteins in appropriate host cells. The peptides, proteins, fusion proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides, proteins and fusion proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides, proteins and fusion proteins in hybridization assays is also described.

=> log y

U.S. Patent & Trademark Office LOGOFF AT 14:16:04 ON 06 APR 95

+++

OK

ATZ

ATZ

OK

ATH

ATH

OK

102390

32 HEK
14345 293

L1 5 HEK(W)293
=> s l1 and homologous(w)recombination
7089 HOMOLOGOUS
9380 RECOMBINATION
482 HOMOLOGOUS(W)RECOMBINATION
L2 1 L1 AND HOMOLOGOUS(W)RECOMBINATION
=> d l1 cit,ab

1. 5,468,615, Nov. 21, 1995, Binding assay employing a synthetic gene for D4 dopamine receptors; Christopher L. Chio, et al., 435/7.2, 6, 69.1; 436/501; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,468,615 [IMAGE AVAILABLE] L1: 1 of 5

ABSTRACT:

A modified gene coding for the human D4 dopamine receptor has been synthesized by chemo-enzymatic methods. The nucleotide sequence of the D4 dopamine receptor gene was changed to reduce the G+C content and to eliminate intronic sequences, while maintaining the published amino acid sequence. Using gene splicing by overlap extension and PCR amplification of long oligonucleotides (>200 bases), 3 synthetic fragments of about 400 base pairs each were amplified, from which the full length gene was assembled. Stable expression of this gene has been achieved in CHO-K1 cells, using an inducible expression system, and in HEK293 cells.
=> d l2 kwic

US PAT NO: 5,468,615 [IMAGE AVAILABLE] L2: 1 of 1

DRAWING DESC:

DRWD(8)

FIG. 4. Scatchard analysis of (.sup.3 H)-spiperone binding in **HEK** **293** D4-24 cells.

DRAWING DESC:

DRWD(10)

FIG. 5. Stable expression of D4 receptors in **HEK** **293** D4-24 cells.

DRAWING DESC:

DRWD(11)

.sup.3 H-spiperone binding at 540 pM was determined in membranes prepared from **HEK** **293** D4-24 cells harvested at the indicated passage.

NETDESC:

This Page is inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images
problems checked, please do not report the
problems to the IFW Image Problem Mailbox**